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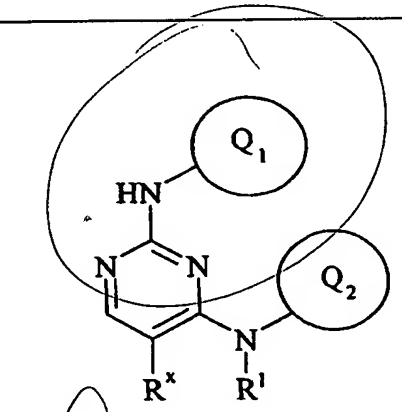
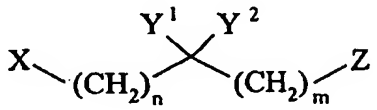
(54) Title: PYRIMIDINE COMPOUNDS

(57) Abstract

A pyrimidine derivative of formula (I): wherein: R^1 is an optional substituent as defined within; R^x is selected from halo, hydroxy, nitro, amino, cyano, mercapto, carboxy, sulphamoyl, formamido, ureido or carbamoyl or a group of formula (Ib): A–B–C– as defined within; Q_1 and Q_2 are independently selected from aryl, a 5– or 6–membered monocyclic moiety; and a 9– or 10–membered bicyclic heterocyclic moiety; and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of formula (Ia) as defined within; and Q_1 and Q_2 are optionally further substituted; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof; are useful as anti–cancer agents; and processes for their manufacture and pharmaceutical compositions containing them are described.



(I)



(Ia)

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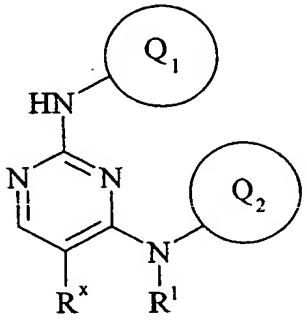
CLAIMS

What we claim is:

1. A pyrimidine derivative of the formula **(I)**:



(I)

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl [optionally substituted by one or two substituents independently selected from halo, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, hydroxy, cyano, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, carbamoyl, -NHCOC$_{1-4}$alkyl, trifluoromethyl, phenylthio, phenoxy, pyridyl, morpholino], benzyl, 2-phenylethyl, C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent, or one phenyl substituent], *N*-phthalimido-C_{1-4}alkyl, C_{3-5}alkynyl [optionally substituted by one phenyl substituent] and C_{3-6}cycloalkyl-C_{1-6}alkyl;

wherein any phenyl or benzyl group in R^1 is optionally substituted by up to three substituents independently selected from halo, hydroxy, nitro, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, cyano, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, mercapto, C_{1-3}alkylthio, carboxy, C_{1-3}alkoxycarbonyl;

R^x is selected from halo, hydroxy, nitro, amino, cyano, mercapto, carboxy, sulphamoyl, formamido, ureido or carbamoyl or a group of formula **(Ib)**:

A-B-C-

(Ib)

wherein:

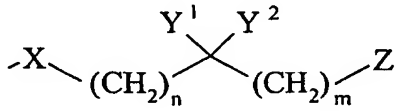
A is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, phenyl, heterocycle or heteroaryl, wherein said C_{1-6}alkyl, C_{3-6}alkenyl and C_{3-6}alkynyl are optionally substituted by one or more substituents selected from halo, nitro, cyano, amino, hydroxy, mercapto, carboxy, formamido, ureido, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, C_{1-3}alkoxy, trifluoromethyl, C_{3-8}cycloalkyl, phenyl, heterocycle or heteroaryl; wherein any phenyl, C_{3-8}cycloalkyl, heterocycle or heteroaryl may be optionally substituted by one or more halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, formamido, ureido, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{1-4}alkanoylamino, *N*-C_{1-4}alkylcarbamoyl, *N,N*-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl and C_{1-4}alkoxycarbonyl;

B is -O-, -S-, -C(O)-, -NH-, -N(C_{1-4}alkyl)-, -C(O)NH-, -C(O)N(C_{1-4}alkyl)-, -NHC(O)-, -N(C_{1-4}alkyl)C(O)- or B is a direct bond;

C is C_{1-4}alkylene or a direct bond;

$\mathbf{Q_1}$ and $\mathbf{Q_2}$ are independently selected from aryl, a 5- or 6-membered monocyclic moiety (linked via a ring carbon atom and containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur); and a 9- or 10-membered bicyclic heterocyclic moiety (linked via a ring carbon atom and containing one or two nitrogen heteroatoms and optionally containing a further one or two heteroatoms selected from nitrogen, oxygen and sulphur);

and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of the formula **(Ia)** and Q_2 may optionally bear on any available carbon atom further substituents of the formula **(Ia)**:



(Ia)

[provided that when present in Q_1 the substituent of formula **(Ia)** is not adjacent to the -NH- link];

wherein:

X is -CH_2-, -O-, -NH-, -NR^y- or -S- [wherein R^y is C_{1-4}alkyl, optionally substituted by one substituent selected from halo, amino, cyano, C_{1-4}alkoxy or hydroxy];

Y^1 is H, C_{1-4}alkyl or as defined for Z;

Y^2 is H or C_{1-4}alkyl;

Z is R^aO-, R^bR^cN-, R^dS-, $R^eR^fNNR^g$-, a nitrogen linked heteroaryl or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring carbon or a ring nitrogen by C_{1-4}alkyl or C_{1-4}alkanoyl] wherein R^a, R^b, R^c, R^d, R^e, R^f and R^g are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-8}cycloalkyl, and wherein said C_{1-4}alkyl and C_{2-4}alkenyl are optionally substituted by one or more phenyl ;

n is 1, 2 or 3;

m is 1, 2 or 3;

and Q_1 may optionally bear on any available carbon atom up to four substituents independently selected from halo, thio, nitro, carboxy, cyano, C_{2-4}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{2-4}alkynyl, C_{1-5}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, amino-C_{1-3}alkyl, C_{1-4}alkylamino-C_{1-3}alkyl, di-(C_{1-4}alkyl)amino-C_{1-3}alkyl, cyano-C_{1-4}alkyl, C_{2-4}alkanoyloxy-C_{1-4}-alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, carboxy-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl-C_{1-4}alkyl, carbamoyl-C_{1-4}alkyl, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkyl, pyrrolidin-1-yl-C_{1-3}alkyl, piperidino-C_{1-3}alkyl, piperazin-1-yl-C_{1-3}alkyl, morpholino-C_{1-3}alkyl, thiomorpholino-C_{1-3}alkyl, imidazo-1-yl-C_{1-3}alkyl, piperazin-1-yl, morpholino, thiomorpholino, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, hydroxyC_{2-4}alkylthio, hydroxyC_{2-4}alkylsulphinyl, hydroxyC_{2-4}alkylsulphonyl, ureido, *N'*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)ureido, *N'*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{2-4}alkanoylamino, sulphamoyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl;

and also independently, or where appropriate in addition to, the above substituents, Q_1 may optionally bear on any available carbon atom up to two further substituents independently selected from C_{3-8}cycloalkyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenylthio, phenyl, naphthyl, benzoyl, benzimidazol-2-yl, phenoxy and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, phenoxy, 5- or

6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-C_{1-4}alkyl, phenylthio and phenyl-C_{1-4}alkoxy substituents may optionally bear up to five substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy;

and Q_2 may optionally bear on any available carbon atom up to four substituents independently selected from halo, hydroxy, thio, nitro, carboxy, cyano, C_{2-4}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{2-4}alkynyl, C_{1-5}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, amino-C_{1-3}alkyl, C_{1-4}alkylamino-C_{1-3}alkyl, di-(C_{1-4}alkyl)amino-C_{1-3}alkyl, cyano-C_{1-4}alkyl, C_{2-4}alkanoyloxy-C_{1-4}-alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, carboxy-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl-C_{1-4}alkyl, carbamoyl-C_{1-4}alkyl, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkyl, pyrrolidin-1-yl-C_{1-3}alkyl, piperidino-C_{1-3}alkyl, piperazin-1-yl-C_{1-3}alkyl, morpholino-C_{1-3}alkyl, thiomorpholino-C_{1-3}alkyl, imidazo-1-yl-C_{1-3}alkyl, piperazin-1-yl, morpholino, thiomorpholino, C_{1-4}alkoxy, cyano-C_{1-4}alkoxy, carbamoyl-C_{1-4}alkoxy, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkoxy, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkoxy, 2-aminoethoxy, 2-C_{1-4}alkylaminoethoxy, 2-di-(C_{1-4}alkyl)aminoethoxy, C_{1-4}alkoxycarbonyl-C_{1-4}alkoxy, halo-C_{1-4}alkoxy, 2-hydroxyethoxy, C_{2-4}alkanoyloxy-C_{2-4}alkoxy, 2-C_{1-4}alkoxyethoxy, carboxy-C_{1-4}alkoxy, 2-pyrrolidin-1-yl-ethoxy, 2-piperidino-ethoxy, 2-piperazin-1-yl-ethoxy, 2-morpholino-ethoxy, 2-thiomorpholino-ethoxy, 2-imidazo-1-yl-ethoxy, C_{3-5}alkenyloxy, C_{3-5}alkynyloxy, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, hydroxyC_{2-4}alkylthio, hydroxyC_{2-4}alkylsulphinyl, hydroxyC_{2-4}alkylsulphonyl, ureido, *N'*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)ureido, *N'*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{2-4}alkanoylamino, sulphamoyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl,

and also independently, or where appropriate in addition to, the above optional substituents, Q_2 may optionally bear on any available carbon atom up to two further substituents independently selected from C_{3-8}cycloalkyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenylthio, phenyl, naphthyl, benzoyl, phenoxy, benzimidazol-2-yl, and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl,

benzoyl, phenoxy, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-C_{1-4}alkyl, phenylthio and phenyl-C_{1-4}alkoxy substituents may optionally bear one or two substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

2. A pyrimidine derivative according to claim 1 wherein R^1 is hydrogen, methyl, $-CH_2CH_2CH_2CF_3$, $-CH_2CH=CHBr$, $-CH_2CH=CHPh$; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

3. A pyrimidine derivative according to claims 1 or 2 wherein R^x is selected from fluoro, chloro, bromo, nitro, amino, cyano, carboxy, methyl, methoxy, ethoxy, ethoxymethyl, vinyl, allyloxymethyl, hydroxymethyl, 2-hydroxyethoxymethyl, 4-hydroxybutoxymethyl, dimethylaminomethyl, diethylaminomethyl, ureidomethyl, formamidomethyl, methylaminomethyl, isopropylaminocarbonyl, phenyl, benzyl, phenethyl, benzoylamino, 4-phenylbutyryl, 2-phenylvinyl (optionally substituted by fluoro), benzyloxymethyl, cyclohexyloxymethyl, 3-cyclopentylpropionyl, morpholino, furyl, imidazolylmethyl, isoxazolyloxymethyl (optionally substituted by methyl), quinolinylaminomethyl, benzothienylaminomethyl, pyrazolylaminomethyl, isoxazolylaminomethyl, thiazolylthiomethyl and tetrazolylthiomethyl; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

4. A pyrimidine derivative according to any one of claims 1 to 3 wherein Q_1 and Q_2 are selected from phenyl, pyridyl, indanyl, indazolyl, indolyl, quinolyl, pyrazolyl or thiazolyl; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

5. A pyrimidine derivative according to any one of claims 1 to 4 wherein the substituent of formula **(Ia)** is 3-amino-2-hydroxypropoxy, 3-methylamino-2-hydroxypropoxy, 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-ethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy, 3-isopropylaminopropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxy-2-methylpropoxy, 3-isobutylamino-2-hydroxypropoxy, 3-*t*-butylamino-2-hydroxypropoxy,

3-ethoxy-2-hydroxypropoxy, 3-(*N*-isopropyl-*N*-benzylamino)-2-hydroxypropoxy, 3-(*N*-allyl-*N*-methylamino)-2-hydroxypropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-methylpiperazin-1-yl)-2-hydroxypropoxy, 3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy, 3-morpholinopropoxy, 3-morpholino-2-hydroxypropoxy, 3-cyclopentylamino-2-hydroxypropoxy, 3-pyrrolidin-1-yl-2-hydroxypropoxy, 3-imidazol-1-ylpropoxy, 3-(*N'*,*N'*-dimethylhydrazino)-2-hydroxypropoxy, 3-*N'*,*N'*-dimethylaminopropylamino, 3-*N'*,*N'*-dimethylamino-2,2-dimethylpropylamino, 3-*N'*,*N'*-dimethylamino-2-hydroxy-*N*-methylpropylamino, 3-*N'*-isopropylaminopropylamino or 3-imidazol-1-ylpropylamino; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

6. A pyrimidine derivative according to any one of claims 1 to 5 wherein Q_2 is optionally substituted by halo, hydroxy, cyano, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, morpholino, C_{1-4}alkoxy, 2-morpholino-ethoxy, 2-imidazo-1-yl-ethoxy, C_{1-4}alkylthio, carbamoyl, amino, C_{2-4}alkanoylamino, sulphamoyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenyl and phenoxy; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

7. A pyrimidine derivative according to any one of claims 1 to 6 wherein Q_1 is optionally substituted by halo; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

8. A pyrimidine derivative according to any one of claims 1 to 7 wherein the substituent of formula **(Ia)** is on Q_1; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

9. A pyrimidine derivative according to any one of claims 1 to 8 which is:
5-bromo-2-{4-[2-hydroxy-3-(*N*,*N*-dimethylamino)propoxy]anilino}-4-anilinopyrimidine;
5-bromo-2-{4-[2-hydroxy-3-(*N*,*N*-dimethylamino)propoxy]anilino}-4-(pyrid-2-ylamino)pyrimidine;
5-bromo-2-{4-[2-hydroxy-3-(isopropylamino)propoxy]anilino}-4-(6-methylpyrid-2-ylamino)pyrimidine;

5-bromo-2-{4-[3-(isopropylamino)propoxy]anilino}-4-anilinopyrimidine;

5-bromo-2-{4-[3-(imidazol-1-yl)propoxy]anilino}-4-(6-methylpyrid-2-ylamino)pyrimidine;

or

4-anilino-5-bromo-2-{4-[2-hydroxy-2-methyl-3-(isopropylamino)propoxy]anilino}pyrimidine

or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

10. A pyrimidine derivative according to any one of claims 1 to 8 which is:

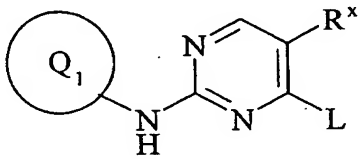
5-bromo-2-{4-[2-hydroxy-3-(*N*,*N*-dimethylamino)propoxy]anilino}-4-(4-chloroanilino) pyrimidine; or

5-bromo-2-{4-[2-hydroxy-3-(*N*,*N*-dimethylamino)propoxy]anilino}-4-[*N*-(4,4,4-trifluorobutyl)anilino]pyrimidine;

or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

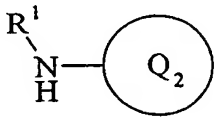
11. A process for preparing a pyrimidine derivative of the formula **(I)** which comprises of:-

a) reacting a pyrimidine of formula **(II)**:



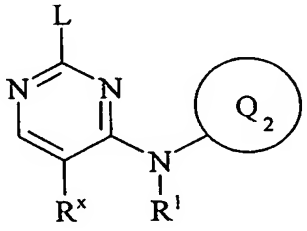
(II)

wherein L is a displaceable group, with a compound of formula **(III)**:



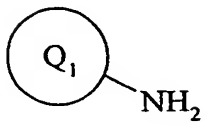
(III)

b) reaction of a pyrimidine of formula **(IV)**:



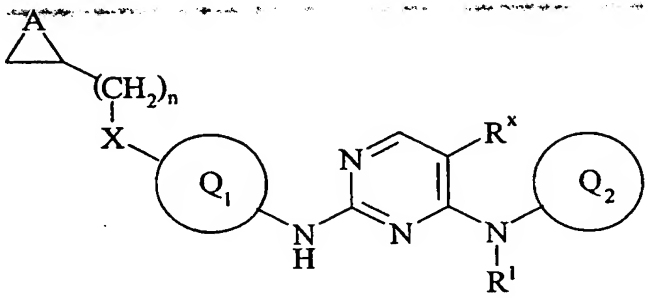
(IV)

wherein L is a displaceable group, with a compound of formula **(V)**:



(V)

c) for compounds of formula **(I)** where n is 1, 2 or 3, m = 1, Y^2 is H and Y^1 is OH, NH_2 or SH by reaction of a 3-membered heteroalkyl ring of formula **(VI)**:



(VI)

wherein A is O, S or NH; with a nucleophile of formula **(VII)**:

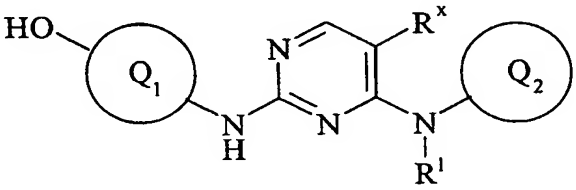
Z-D

(VII)

wherein D is H or a suitable counter-ion;

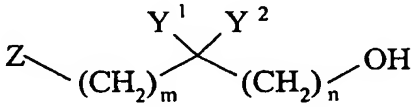
d) for compounds of formula **(I)** where X is oxygen:

by reaction of an alcohol of formula **(VIII)**:



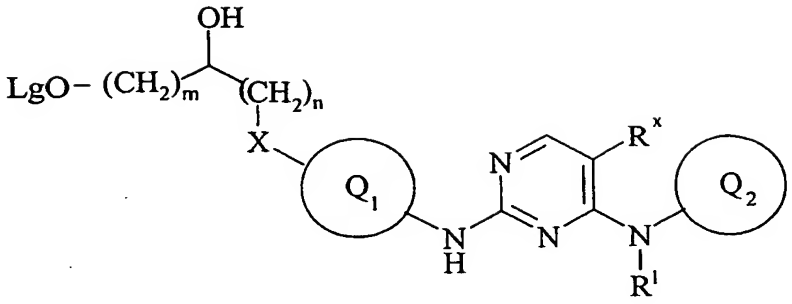
(VIII)

with an alcohol of formula **(IX)**:



(IX)

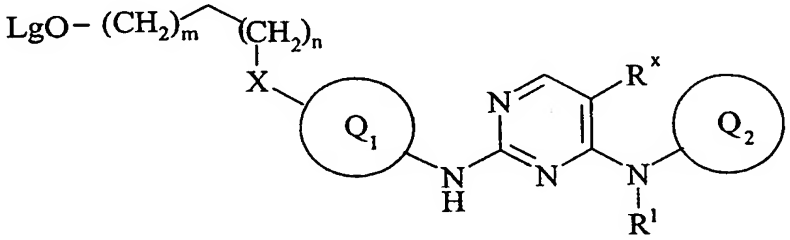
e) for compounds of formula **(I)** wherein X is $-CH_2-$, -O-, -NH- or -S-, Y^1 is OH, Y^2 is H and m is 2 or 3; reaction of a compound of formula **(X)**:



(X)

wherein LgO is a leaving group; with a nucleophile of formula **(VII)**;

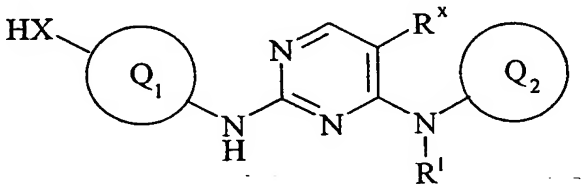
f) for compounds of formula **(I)** wherein X is $-CH_2-$, -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula **(XI)**:



(XI)

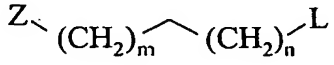
wherein LgO is a leaving group; with a nucleophile of formula **(VII)**;

g) for compounds of formula **(I)** wherein X is -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula **(XII)**:



(XII)

with a compound of formula **(XIII)**



(XIII)

wherein L is a displaceable group;

h) for compounds of formula **(I)** in which Z is HS-, by conversion of a thioacetate group in a corresponding compound;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

12. A method for producing an anti-cancer effect in a warm blooded animal which comprises administering to said animal an effective amount of a pyrimidine derivative of the formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt, or *in vivo* hydrolysable ester thereof.

13. The use of a pyrimidine derivative of the formula (I) according to any one of claims 1 to 10, or a pharmaceutically-acceptable salt, or *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm blooded animal.

14. A pharmaceutical composition which comprises a pyrimidine derivative of the formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04325

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/48 C07D401/12 C07D239/50 A61K31/505 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 95, no. 11, 1981 Columbus, Ohio, US; abstract no. 97712f, GHOSH,D.: "2,4-BIS(ARYLAMINO)-6-METHYLPYRIMIDINES AS ANTIMICROBIAL AGENTS" page 648; XP002109184 abstract & J.INDIAN CHEM. SOC., vol. 58, no. 5, 1981, pages 512-13, INDIA	1,14
A	WO 91 18887 A (SMITH KLINE) 12 December 1991 (1991-12-12) page 38; claims	1,14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2000	14/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04325

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 99 50250 A (JANSSEN) 7 October 1999 (1999-10-07) the whole document	1,14

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/04325

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9118887 A	12-12-1991	AU 7971691 A	31-12-1991
WO 9950250 A	07-10-1999	AU 3599699 A	18-10-1999
		EP 0945443 A	29-09-1999
		EP 0945442 A	29-09-1999

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